(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 October 2003 (16.10.2003)

PCT

(10) International Publication Number
WO 03/084610 A1

(51) International Patent Classification⁷: A61P 25/18, A61K 45/06, 31/551, 31/196

(21) International Application Number: PCT/US03/07283

(22) International Filing Date: 21 March 2003 (21.03.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/369,771 3 April 2002 (03.04.2002) US
60/369,797 3 April 2002 (03.04.2002) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK (utility model), SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *of inventorship (Rule 4.17(iv)) for US only*

Published:

— *with international search report*

[Continued on next page]

(54) Title: THERAPY FOR PSYCHOSES COMBINING AN ATYPICAL ANTIPSYCHOTIC AND AN MGLU2/3 RECEPTOR AGONIST

(57) Abstract: The present invention provides for a pharmaceutical composition and methods for treating psychosis comprising the combination or a first component which is an atypical antipsychotic with a second component which is a mGlu2/3 receptor agonist. The present invention also provides for a pharmaceutical composition and method of treating a psychiatric disorder comprising the combination of a first component which is an atypical antipsychotic with a second component which is a compound which allosterically enhances receptor activity for mGlu2 and/or mGlu3.

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While all combinations of first and second component compounds are useful and valuable, certain combinations and methods of administration are particularly valued and are preferred.

Preferred combinations which include clozapine as a first component are:

Clozapine / LY379268;

Clozapine / LY404039;

Clozapine / LY459477;

Clozapine / LY354740;

Clozapine / (1S,2S,5R,6S)-2-[(2'S)-(2'Amino)-propionyl]amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid hydrochloride salt (oral); and

Clozapine /(1S,2R,4S,5S,6S)-4-[(2'S)-(2'-Amino)-propionyl]amino-(2-fluorobicyclo[3.1.0]hexane)-2,6-dicarboxylic acid hydrochloride.

Preferred combinations which include olanzapine as a first component are:

Olanzapine / LY379268;

Olanzapine / LY404039;

Olanzapine / LY459477;

Olanzapine / LY354740;

Olanzapine /(1S,2S,5R,6S)-2-[(2's)-(2'-Amino)-propionyl]amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid hydrochloride salt (oral); and

Olanzapine /(1S,2R,4S,5S,6S)-2-[(2'S)-(2'-Amino)-propionyl]amino-(4-fluorobicyclo[3.1.0]hexane)-2,6-dicarboxylic acid hydrochloride (oral).

In general, combinations and methods of treatment using clozapine or olanzapine as the first component are preferred. Furthermore, combinations and methods of treatment using LY404039 as the second component are preferred.

Furthermore, in general, it will be understood that alternative formulations to deliver components of the instant invention, particular mGlu2/3 agonists, may be accomplished via prodrugs, particularly peptidyl prodrugs.

It will be understood by the skilled reader that most or all of the compounds used in the present invention are capable of forming salts, and that the salt forms of pharmaceuticals are commonly used, often because they are more readily crystallized and purified than are the free bases. In all cases, the use of the pharmaceuticals described above as salts is contemplated in the description herein, and often is preferred, and the pharmaceutically acceptable salts of all of the compounds are included in the names of them.

Many of the compounds used in this invention are amines, and accordingly react with any of a number of inorganic and organic acids to form pharmaceutically acceptable acid addition salts. Since some of the free amines of the compounds of this invention are typically oils at room temperature, it is preferable to convert the free amines to their pharmaceutically acceptable acid addition salts for ease of handling and administration, since the latter are routinely solid at room temperature. Acids commonly employed to form such salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids, such as p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid and the like. Examples of such pharmaceutically acceptable salts thus are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, hydroxybutyrate, glycollate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like. Preferred pharmaceutically acceptable salts are those formed with hydrochloric acid, oxalic acid or fumaric acid.

Administration

The dosages of the drugs used in the present invention must, in the final analysis, be set by the physician in charge of the case, using knowledge of the drugs, the properties

We claim:

1. A pharmaceutical composition which comprises a first component which is an atypical antipsychotic and a second component which is mGlu2/3 receptor agonist.

2. A method for treating a patient suffering from or susceptible to a psychiatric disorder, comprising administering to said patient an amount of a first component which is an atypical antipsychotic, in combination with an amount of a second component which is a mGlu2/3 receptor agonist.

3. A pharmaceutical composition which comprises a first component which is clozapine and a second component which is (1R,4S,5S,6S)-4-[(2'S)-(2'-Amino)-propionyl]amino-(2-sulfonylbicyclo[3.1.0]hexane)-4,6-dicarboxylic acid.

4. A method for treating a patient suffering from or susceptible to a psychiatric disorder, comprising administering to said patient an amount of a first component which is clozapine, in combination with an amount of a second component which is (1R,4S,5S,6S)-4-[(2'S)-(2'-Amino)-propionyl]amino-(2-sulfonylbicyclo[3.1.0]hexane)-4,6-dicarboxylic acid.

5. A pharmaceutical composition which comprises a first component which is clozapine and a second component which is (1R, 4R, 5S, 6R)-4-amino-(2-oxabicyclo[3.1.0]hexane)-4,6-dicarboxylic acid.

6. A method for treating a patient suffering from or susceptible to a psychiatric disorder, comprising administering to said patient an amount of a first component which is clozapine, in combination with an amount of a second component which is (1R, 4R, 6S, 6R)-4-amino-(2-oxabicyclo[3.1.0]hexane)-4,6-dicarboxylic acid.

7. A pharmaceutical composition which comprises a first component which is clozapine and a second component which is (1S, 2R, 4S, 5S, 6S)-2-amino-4-fluoro bicyclo[3.1.0]hexane-2,6-dicarboxylic acid.

8. A method for treating a patient suffering from or susceptible to a psychiatric disorder, comprising administering to said patient an amount of a first component which is clozapine in combination with an amount of a second component which is (1S, 2R, 4S, 5S, 6S)-2-amino-4-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid.

9. A pharmaceutical composition which comprises a first component which is clozapine and a second component which is (+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid.

10. A method for treating a patient suffering from or susceptible to a psychiatric disorder, comprising administering to said patient an amount of a first component which is clozapine in combination with an amount of a second component which is (+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid.

11. A pharmaceutical composition which comprises a first component which is olanzapine and a second component which is (1R,4S,5S,6S)-4-[(2'S)-(2'-Amino)-propionyl]amino-(2-sulfonylbicyclo[3.1.0]hexane)-4,6-dicarboxylic acid.

12. A method for treating a patient suffering from or susceptible to a psychiatric disorder, comprising administering to said patient an amount of a first component which is olanzapine in combination with an amount of a second component which is (1R,4S,5S,6S)-4-[(2'S)-(2'-Amino)-propionyl]amino-(2-sulfonylbicyclo[3.1.0]hexane)-4,6-dicarboxylic acid.

13. A pharmaceutical composition which comprises a first component which is olanzapine and a second component which is (1R, 4R, 5S, 6R)-4-amino-(2-oxabicyclo [3.1.0]hexane)-4,6-dicarboxylic acid.

14. A method for treating a patient suffering from a susceptible to a psychiatric disorder, comprising administering to said patient an amount of a first

component which is olanzapine in combination with an amount of a second component which is (1R, 4R, 5S, 6R)-4-amino-(2-oxabicyclo [3.1.0]hexane)-4,6-dicarboxylic acid.

15. A pharmaceutical composition which comprises a first component which is olanzapine and a second component which is (1S, 2R, 4S, 6S)-2-amino-4-fluorobicyclo[3.1.0]hexane –2,6-dicarboxylic acid.

16. A method for treating a patient suffering from or susceptible to a psychiatric disorder, comprising administering to said patient an amount of a first component which is olanzapine in combination with an amount of a second component which is (1S, 2R, 4S, 6S)-2-amino-4-fluorobicyclo[3.1.0]hexane –2,6-dicarboxylic acid.

17. A pharmaceutical composition which comprises a first component which is olazapine and a second component which is (+)-2-aminobicyclo[3.1.0] hexane –2,6-dicarboxylic acid.

18. A method for treating a patient suffering from or susceptible to a psychiatric disorder, comprising administering to said patient an amount of a first component which is olanzapine in combination with an amount of a second component which is (+)-2-aminobicyclo[3.1.0] hexane –2,6- dicarboxylic acid.

19. A pharmaceutical composition which comprises a first component which is an atypical antipsychotic and a second component which is a compound which allosterically enhances receptor activity for mGlu2 or mGlu3.

20. A method for treating a patient suffering from or susceptible to a psychiatric disorder, comprising administering to said patient an amount of a first component which is an atypical antipsychotic in combination with an amount of a second component which is a compound which allosterically enhances receptor activity for mGlu2 or mGlu3.

21. A pharmaceutical composition which comprises a first component which is an atypical antipsychotic and a second component which is a compound which allosterically enhances receptor activity for mGlu2 and mGlu3.

22. A method for treating a patient suffering from or susceptible to a psychiatric disorder, comprising administering to said patient an amount of a first component which is an atypical antipsychotic in combination with an amount of a second component which is a compound which allosterically enhances receptor activity for mGlu2 and mGlu3.